Differential Effects of the Tricyclic Antidepressant Desipramine on the Density of Adrenergic Receptors in Juvenile and Adult Rats

Jean D. Deupree, Abbey L. Reed, and David B. Bylund
Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, Nebraska
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ABSTRACT
Although the tricyclic antidepressants, such as desipramine (DMI), are among the most efficacious treatments for adult depression, they are not effective in treating childhood and adolescent depression. Because the adrenergic nervous system is not fully developed until late adolescence, we hypothesized that the mechanisms regulating receptor density may not yet be mature in young mammals. To test this hypothesis, the effects of DMI treatment on cortical $\beta_{1}$-, $\beta_{2}$-, and $\alpha_{2}$-adrenergic receptors were compared in juvenile and adult rats. DMI was delivered either by 4 days of twice daily injections to postnatal day 9 to 13 (4 and 7 mg/kg/day) and adult (20 mg/kg/day) rats, or by 2 weeks of continual drug infusion (osmotic minipumps) to postnatal day 21-35 (15 mg/kg/day) and adult (10 mg/kg/day) rats. These delivery paradigms gave juvenile brain concentrations of DMI similar to those in adult rats. The $\beta_{2}$-adrenergic receptor was down-regulated with both treatment paradigms in both juvenile and adult rats. By contrast, in the postnatal day 9 to 13 rats, there was a dose-dependent up-regulation of the $\beta_{1}$-1 in the cortex and $\beta_{1}$-2-adrenergic receptor in the prefrontal cortex, whereas there was no change in density in adult rats. These differences in the $\beta_{1}$-adrenergic receptor regulation after DMI treatment suggest that the lack of efficacy of tricyclic antidepressants in treating childhood depression may be related to immature regulatory mechanisms for these receptors.

Major depressive disorder in children and adolescents is a debilitating and serious mental illness that has a detrimental effect on the well being of life for those affected with this disorder. It is one of the most common mental health disorders in this population, with a prevalence in children of up to 2.5% (Birmaher et al., 1996) and between 4 and 8% in adolescents (Kessler et al., 2001). There is a 25% chance that a child will have had an episode of major depression by the time he or she reaches adulthood (Kessler et al., 2001). Although the tricyclic antidepressants, such as desipramine (DMI), are among the most efficacious treatments for adult depression, in most controlled studies they are not more effective than placebo in treating childhood and adolescent depression (Ambrosini, 2000; Weller and Weller, 2000). By contrast, the selective serotonin reuptake inhibitors, particularly fluoxetine, do seem to be effective (March et al., 2004; Kratochvil et al., 2006). The lack of response to tricyclic antidepressants may relate to the immature nature of the nervous system, because the human brain is not fully developed until early adulthood (Blakemore and Choudhury, 2006). Indeed, the noradrenergic system develops more slowly than the serotonergic system (Murrin et al., 2007).

DMI is a tricyclic antidepressant that is selective for the norepinephrine transporter. The immediate effect of DMI is an inhibition of the norepinephrine transporter (NET), resulting in an increase in norepinephrine in the synaptic cleft. However, the antidepressant effects of DMI occur with a longer time course of administration, and they may be related to adrenergic receptor down-regulation as is seen consistently with the $\beta_{2}$-adrenergic receptor (Scott and Crews, 1983; Beer et al., 1987; Sethy et al., 1988; Argenti and D’Mello, 1994b; Goodnough and Baker, 1994).

This article reports the effects of DMI on adrenergic receptor regulation in juvenile rats at postnatal day (PND) 9 to 13 and 21 to 35 compared with adult rats. Sexual maturity in rats occurs at about PND 35, corresponding roughly to puberty or early adolescence. In rats, there is a dramatic increase in synaptogenesis, adrenergic receptor density and NET formation between PND 10 and 20 (Murrin et al., 2007).
In many areas, these receptors are at their highest levels around PND 20 to 30 after which they decline to adult levels. The development of NET follows a similar pattern. These developmental changes in the noradrenergic system in juvenile rats suggest that juveniles and adults have different adrenergic receptor regulatory mechanisms. Indeed, the results reported here indicate that DMI down-regulates the α-1 and α-2-adrenergic receptors in juvenile rats in a manner that is similar to that seen in adults, but there are differences in how the α-1 and α-2-adrenergic receptors are regulated between juvenile and adult rats.

Materials and Methods

Materials. DMI was obtained from Sigma-Aldrich (St. Louis, MO). Desmethyl-desipramine (DDMI) was provided by the National Institutes of Health (NIH). Procedures were in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of Nebraska Medical Center Animal Care Committee. Adult rats were from Durect Corporation. The animals were anesthetized and then stored frozen at −80°C until assayed for receptor density. The cerebellum was used for the measurement of DMI and DDMI concentrations.

Brain DMI and DDMI Concentration Measurements. Cerebellum was weighed and homogenized for 30 to 60 s at 16,000 rpm by using a Tissuemizer Ultra Turrax (IKA Works, Inc., Wilmington, NC) in 20 volumes of water. Serum and tissue samples were alkalized with 1 M sodium carbonate. An internal standard (McN-IR-1854; chlorohaloperidol) was added to each sample before extraction into 1% isomyl alcohol in hexane solution. The organic layers were further extracted into 20 mL phosphoric acid. Samples were separated on an Alltech Adsorbosphere C18 column (HS 3u; 150 by 4.6 mm; Alltech Associates, Deerfield, IL) using 50 mL phosphate buffer, pH 7.2, 50% acetonitrile, and 0.01% dimethyloctylamine mobile phase, and they were detected at 252 nm.

TABLE 1

Assay conditions for the saturation assays for the three adrenergic receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>α-1-Adrenergic</th>
<th>α-2-Adrenergic</th>
<th>β-Adrenergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiisotope</td>
<td>[3H]Prazosin</td>
<td>[3H]RX821002</td>
<td>[125I]Iodopindolol</td>
</tr>
<tr>
<td>Nonspecific binding</td>
<td>0.2 mM Norepinephrine</td>
<td>0.2 mM norepinephrine</td>
<td>1 μM isoproterenol</td>
</tr>
<tr>
<td>Assay volume</td>
<td>4.0 ml</td>
<td>1.0 ml</td>
<td>0.25 mL</td>
</tr>
<tr>
<td>Assay buffer</td>
<td>25 mM Sodium phosphate, pH 7.4</td>
<td>25 mM Sodium phosphate, pH 7.4</td>
<td>25 mM Sodium phosphate, pH 7.4</td>
</tr>
<tr>
<td>Incubation time</td>
<td>1 h at room temperature</td>
<td>1 h at room temperature</td>
<td>1 h at room temp</td>
</tr>
</tbody>
</table>

* Methods used were similar to those reported previously (Deupree et al., 1996).
* Serial dilutions were prepared in 0.5 mM HCl.
* Serial dilutions were prepared in water.
Results

Adrenergic Receptor Density after 4 Days of DMI Administration. Adults rats were given 10 mg/kg twice daily for 4 days, a treatment paradigm that has previously been shown to down-regulate the β-adrenergic receptor (Argenti and D'Mello, 1994a). To compare the effects of DMI administration on adrenergic receptor density in juvenile rats with that seen with adult rats, it was first necessary to ensure that the dose of DMI given to the juvenile rats would produce brain DMI concentrations that were comparable with those produced in adult rats. Furthermore, DMI is demethylated in rats to DDMI, which is equipotent with DMI in down-regulating β-adrenergic receptors (Argenti and D'Mello, 1994b). The appropriate dose of DMI to give juvenile rats so that the brain DMI and DDMI concentrations are comparable with those in adult rats has been determined previously (Kozisek et al., 2007). These results indicated that the PND 9 to 12 rats needed between 4 and 7 mg/kg/day in two divided doses to give brain concentrations comparable with those seen in adult rats receiving 20 mg/kg/day. Accordingly, adult (10 mg/kg/injection) and PND 9 to 12 (2.0 and 3.5 mg/kg/injection) rats were injected i.p. twice a day for 4 days, and the brains removed 12 h after the last injection. The DMI concentrations in the PND 13 rats were one half (4 mg/kg/day) and twice (7 mg/kg/day) that obtained in adult rats given 20 mg/kg/day, whereas the DDMI concentrations in the juveniles were lower (Table 2).

The binding site densities of α-1-, α-2-, and β-adrenergic receptors in the prefrontal cortex and remainder of cortex (cortex) were determined using membrane saturation binding experiments. The α-1-adrenergic receptor densities in the prefrontal cortex were not measured in the juvenile or adult rats due to the lack of sufficient tissue for all three receptor binding assays. The α-1- and α-2-adrenergic receptor densities were increased in the cortex and prefrontal cortex, respectively, of the PND 13 rats in a dose-dependent manner, with the 7 mg/kg/day dose being significantly different from the control values after 4 days of twice daily injections of DMI (Fig. 1; Table 3). By contrast, DMI treatment did not alter the α-1- or α-2-adrenergic receptor densities in the adult rats. In the control adult rats the α-2 receptor density was 128% higher in the prefrontal cortex than in the rest of the cortex.

The receptor densities for the control PND 13 rats were the same in both of these cortical areas. DMI produced a 27 to 52% down-regulation of the β-adrenergic receptor in both adult and juvenile prefrontal and cortex at all doses (p < 0.05) (Fig. 1; Table 3). There was no significant difference between β-adrenergic receptor den-
sities in the prefrontal cortex and remainder of cortex for either the control adult or juvenile brains. The affinities of the radioligand for their respective receptors did not differ with age of rat or dose of drug given (Table 4).

**Adrenergic Receptor Density after 2 Weeks of DMI Administration.** DMI was administered by continual subcutaneous infusion using osmotic minipumps to adult (10 mg/kg/day) and to juvenile rats starting at PND 21 (15 mg/kg). The rat brains were removed 14 days later while drug was still being delivered. The juvenile rats were given a higher dose of DMI (15 mg/kg/day) than the adult rats (10 mg/kg/day), because previous studies indicated that the brain concentrations in the PND 21 to 35 rats given 10 mg/kg/day were lower than those of adult rats given the same dose (Kozisek et al., 2007). In the current study, a dose of DMI of 15 mg/kg/day in the PND 21 to 35 rats gave DMI plus DDMI concentrations that were 2.2 times that obtained in the adult rats (Table 2).

DMI decreased the α-1-adrenergic receptor binding after drug delivery to PND 21 to 35 but not to adult rats (Fig. 2; Table 5). DMI did not change the density of the α-2-adrenergic receptors in either the juvenile or adult rats using the 2 weeks of continual drug delivery paradigm (Fig. 2; Table 5). Densities in the cortex and the prefrontal cortex in control animals were not significantly different. DMI produced a down-regulation of the β-adrenergic receptor in adult and juvenile rats of approximately 50% in both the prefrontal cortex and the remainder of the cortex (46 and 48%, respectively) (Fig. 2; Table 5). The density of β-adrenergic receptors in the control rats was similar in prefrontal cortex and the cortex for both adult and PND 35 rats.

**Age-Related Changes in Adrenergic Receptor Density between Prefrontal Cortex and Cortex.** Comparison of the receptor densities of control rats at the different ages indicated that, for both the α-1- and β-adrenergic receptors,

<table>
<thead>
<tr>
<th>Adrenergic Receptor Subtype</th>
<th>4-Day Treatment $K_d$ (pM) $\pm S.E.$</th>
<th>2-Week Treatment $K_d$ (pM) $\pm S.E.$</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-1</td>
<td>8.9 $\pm$ 0.1 (n = 32)</td>
<td>9.7 $\pm$ 0.1 (n = 20)</td>
</tr>
<tr>
<td>α-2</td>
<td>70.7 $\pm$ 1.2 (n = 60)</td>
<td>115 $\pm$ 1 (n = 32)</td>
</tr>
<tr>
<td>β</td>
<td>19.0 $\pm$ 0.3 (n = 61)</td>
<td>15.8 $\pm$ 0.3 (n = 31)</td>
</tr>
</tbody>
</table>

Fig. 2. Changes in adrenergic receptor density following 2 weeks of continual drug delivery to adult and PND 21 to 35 rats. α-1-, α-2-, and β-adrenergic receptor densities were determined using saturation experiments on prefrontal cortex (P) and the remainder of cortex (C) removed from brains while drug was still being delivered to the animal. The values are the mean of binding assays on brain samples from four rats. Statistical significance was determined using the Student’s t test. * $p < 0.05$, significantly different from control for the same age group and brain area. † $p < 0.05$, significantly different for control juvenile brain area compared with the same brain area in the adult rat.

The densities in both the prefrontal cortex and the cortex were lower in PND 13 rats and higher in PND 35 rats compared with adults (Table 6). By contrast, for the α-2 receptor the densities were higher in the cortex at both younger ages and lower in the prefrontal cortex compared with adults (Table 6).
TABLE 5
Percentage of change in adrenergic receptor density in PFC and cortex following 2 weeks of continual DMI delivery compared with controls
The data from the DMI treated animals from Fig. 2 are expressed as a percentage of the control values.

<table>
<thead>
<tr>
<th>Adrenergic Receptor Subtype</th>
<th>10 mg/kg/day DMI to Adult Rats</th>
<th>15 mg/kg/day DMI to PND 21 to 35 Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cortex</td>
<td>PFC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cortex</td>
</tr>
<tr>
<td>α-1</td>
<td>96</td>
<td>N.D.</td>
</tr>
<tr>
<td>α-2</td>
<td>99</td>
<td>103</td>
</tr>
<tr>
<td>β</td>
<td>59*</td>
<td>44*</td>
</tr>
</tbody>
</table>

N.D. indicates areas that were not analyzed.

* Significantly different (p < 0.05) than control animals at same age by using the Student’s t test.

TABLE 6
Comparison of adrenergic receptor densities in the juvenile control rats compared with control adult rats
Binding site densities in juvenile rats are expressed as a percentage of that seen in adult rats.

<table>
<thead>
<tr>
<th>Adrenergic Receptor Subtype</th>
<th>PND 13</th>
<th>PND 35</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cortex</td>
<td>PFC</td>
</tr>
<tr>
<td></td>
<td>Cortex</td>
<td>PFC</td>
</tr>
<tr>
<td>α-1</td>
<td>56*</td>
<td>N.D.</td>
</tr>
<tr>
<td>α-2</td>
<td>110*</td>
<td>81*</td>
</tr>
<tr>
<td>β</td>
<td>70*</td>
<td>71*</td>
</tr>
</tbody>
</table>

N.D. indicates brain areas that were not analyzed.

* Significantly different (p < 0.05) than Bmax values in the control adult rat cerebral samples using the Student’s t test.

Discussion

The central finding of this study is the differential effect of DMI on α-2 and α-1-adrenergic receptor regulation in juvenile rats (PND 9–13) compared with adults. The up-regulation of the α-2 and α-1 receptors is opposite to the predicted down-regulation (in response to increased norepinephrine) and different from the lack of regulation of these receptors in adults. These results support the hypothesis that the lack of response of children and adolescents to DMI relates to the immature nature of the mechanisms regulating the levels of the α-adrenergic receptors, because the adrenergic nervous system is not fully developed. Our results could be interpreted to suggest that other tricyclic antidepressants, such as amitriptyline, which have a significant serotonin component, might be effective in childhood and adolescent depression. However, two small clinical studies found that amitriptyline was no better than placebo in the treatment of adolescent depression (Kye et al., 1996; Birmaher et al., 1998).

The adrenergic nervous system develops more slowly than other neurotransmitter systems (such as the serotonergic system), and the adult patterns of norepinephrine innervation are not reached until the fourth or fifth postnatal week (Murrin et al., 2007). Other studies in our laboratory confirm a lack of response to DMI but not to selective serotonin reuptake inhibitors in juvenile rats. DMI does not produce an antidepressant-like effect in PND 21 animals in either the forced swim test or in the learned helplessness model of depression, whereas juvenile animals do respond to selective serotonin reuptake inhibitors in both paradigms (Maul et al., 2005, 2006). Furthermore, in juvenile animals citalopram, but not DMI, increases hippocampal brain-derived neurotropic factor and up-regulates its receptor TrkB (Kozisek et al., 2006).

Effects of DMI on β-Adrenergic Receptors in Adult Rats. Because DMI inhibits NET, it is expected that the increased concentration of norepinephrine will over time produce adrenergic receptor down-regulation. Down-regulation of the β-adrenergic receptor has been reported with other tricyclic and monoamine oxidase inhibitor antidepressants in adult rats. This is a robust finding that is confirmed once again in our studies. The studies on adult animals confirm that our treatment paradigms are appropriate and that they produce a response similar to that reported by others. DMI has been shown in adult rats to produce down-regulation of the β-adrenergic receptor when it is given either by twice daily injections for 4 days (Argenti et al., 1994b) or by continual infusion for 2 weeks (Beer et al., 1987).

Three factors have been reported to play a role in the extent of down-regulation of the β-adrenergic receptor: 1) dose (Scott and Crews, 1983; Sethy et al., 1988; Argenti and D’Mello, 1994a,b; Goodnough and Baker, 1994), 2) time (Scott and Crews, 1983; Sethy et al., 1988; Argenti and D’Mello, 1994a; Argenti and D’Mello, 1994b; Newman-Tancredi et al., 1996), and 3) concentration of the active metabolite DDMI (Argenti et al., 1994b). Argenti and D’Mello (1994b) have previously shown that the extent of down-regulation of the β-adrenergic receptor following 4 days of DMI injection is dependent on the dose of drug with 20 mg/kg/day producing maximal reduction. At lower doses of DMI, a longer length of treatment is required to produce maximal down-regulation.

Appropriate Doses of DMI for Juvenile Rats. Ideally, to compare the effects of DMI in the adult and juvenile rats, the concentration of active drug at the receptors should be similar regardless of age. Furthermore, it is important to compare both DMI plus DDMI, because DDMI is an active metabolite with a potency that is similar to that of DMI, at least in terms of down-regulating the β-adrenergic receptor (Argenti and D’Mello, 1994b). With the 4-day injection paradigm, the brain concentrations of DMI plus DDMI in the PND 13 rats are 0.3 and 1.2 times (4 and 7 mg/kg/day, respectively) that seen in adult rats (20 mg/kg/day). After continuous delivery of drug, the concentration of DMI + DDMI in PND 35 rats is 2.3 times that seen in adult rats at 1.5 times the dose.

Effects of Chronic DMI Treatment on α-1- and α-2-Adrenergic Receptors in Adult Rats. Published reports on the changes in α-1- and α-2-adrenergic receptor densities following chronic treatment with DMI or other tricyclic antidepressants are inconsistent. One study reported a 2-fold increase in α-1-adrenergic receptor binding in mouse forebrain and hippocampus after 21 days of amitriptyline (10 mg/kg twice daily) treatment but not after 7 and 14 days of treatment (Rehavi et al., 1980). Another study found that the proportion of α-1 receptors in the high-affinity state in the thalamus are increased following 3 weeks of daily i.p. injections of DMI (10 mg/kg) (Menkes et al., 1983). No down-regulation of the α-1-adrenergic receptors was noted following 3 weeks of once daily i.p. injections of 10 mg/kg DMI, a paradigm that down-regulated the β-adrenergic receptor (Tang et al., 1981). Functional α-1 receptor supersensitivity was found in the thalamus following chronic treatment with several tricyclic antidepressants, including DMI (Menkes and Aghajanian, 1981). Our studies did not detect changes in the α-1-adrenergic receptors in the adult cortex with either DMI treatment paradigm.

Several studies have reported down-regulation of the α-2-
adrenergic receptors in adults following chronic antidepressant administration to adult rats. Down-regulation was found in the amygdala, hippocampus, caudate nucleus, hypothalamus, and locus coeruleus after 2 weeks of twice daily injections of the tricyclic antidepressant amitriptyline (Smith et al., 1981b). Treatment with monoamine oxidase inhibitors (clorgyline and tranylcypromine) for 2 h to 14 days resulted in a time-dependent decrease in α-2-adrenergic receptors in the cerebral cortex (Giralt and Garcia-Sevilla, 1989). Forty days of chronic treatment of rats with tricyclic antidepressants, including DMI, produced a down-regulation of both α-1 and α-2-adrenergic receptors in the cortex, but not in the hippocampus (Subhash et al., 2003). However, down-regulation of the α-2 receptor in the cortex was not detected following 3 weeks of once daily i.p. injection of 10 mg/kg DMI (Tang et al., 1981), or in the locus coeruleus following 14 days of once daily injections of 10 mg/kg DMI (Sacchetti et al., 2001).

A major difference between our studies and those reported by others (Smith et al., 1981a; Tang et al., 1981; Subhash et al., 2003) is that we used the radiolabeled antagonist [3H]RX821002, which measures changes in total receptor population (high- and low-affinity states), and the other investigators used the radiolabeled agonist [3H]clonidine, which is more likely to measure changes in high-affinity state of the receptor. Our studies indicate that the total receptor population of α-2-adrenergic receptors does not change in the prefrontal or cortex in the adult rat following either four twice daily injections of a high dose of DMI or 2 weeks of continual drug delivery at a lower dose, which agrees with other studies using the antagonist radioligand (Sacchetti et al., 2001).

Several studies suggest that the α-2-adrenergic receptors are involved in depression and in the effects of tricyclic antidepressants. For example, mice lacking the α-2A-adrenergic receptor had increased immobility and were insensitive to the effects of imipramine in the forced swim test (Schramm et al., 2001). An increase in α-2-adrenergic receptors has been reported in brains of depressed suicide victims (Meana et al., 1992; Callado et al., 1998). Postmortem studies of the locus coeruleus of patients suffering from major depression indicated an increased α-2-adrenergic receptor density compared with control patients (Ordway et al., 2003). Major depression has also been associated with a decreased platelet α-adrenergic receptor density (Maes et al., 1999).

Effects of DMI on Adrenergic Receptor Density in Juvenile Rats. The effects of DMI or other antidepressants on adrenergic receptor densities in juvenile animals have not previously been reported. We found that the β-adrenergic receptor was down-regulated in both groups of juvenile animals in a manner similar to that seen in adult rats. By contrast, we found that the α-adrenergic receptors were regulated differently in the juveniles compared with adults. DMI treatment up-regulated the α-1-adrenergic receptor in the PND 9 to 13 rat cortex and down-regulated it in the PND 21 to 35 rats compared with no change in the adult rats. The α-2-adrenergic receptor density in the prefrontal cortex in the PND 9 to 13 was up-regulated following chronic DMI treatment, but there was no change in the PND 21 to 35 rats or the adult rats.

In contrast to the effects of DMI treatment on receptor density, the affinities of the radioligands for their respective receptors were similar in both ages of juvenile and adult rats. Many other studies have similarly found no change in the affinity of the radioligand for adrenergic receptors following antidepressant treatment (Tang et al., 1981; Argenti and D’Mello, 1994b; Goodnough and Baker, 1994; Subhash et al., 2003).

Adrenergic Receptor Densities in Juveniles Compared with Adults. In most regions of the brain, the α-1-adrenergic receptors are low at birth, increase to adult levels or greater in the first 3 weeks postnatally, and then stabilized at adult levels over the next week (Slotkin et al., 1990). Our studies confirm that the α-1-adrenergic receptor in the cortex (not including prefrontal) is lower than adult levels on PND 13 and exceeds adult levels at PND 35.

The α-2-adrenergic receptor density increases after birth and reaches maximal levels at PND 15 in most regions of the rat brain with major increases occurring between PND 10 and 15 (Happe et al., 2004). This is also a time of rapid development of NET (Sanders et al., 2005) and of high levels of synaptogenesis (Murrin et al., 2007). Autoradiographic studies have found variations in the rate of development of the α-2 receptors throughout the brain (Happe et al., 2004). Consistent with these findings, in our homogenate binding assays the α-2 receptor density was lower in PND 13 cortex and higher in frontal cortex compared with adult rats, whereas the receptor densities in these cortical regions are the same as in the adult rats by PND 35.

The β-adrenergic receptor density in the rat cerebral cortex is low at birth and increase rapidly in density in the second postnatal week to greater than adult levels by PND 15 to 21, and then it declines to adult levels over the next several months (Harden et al., 1977; Pittman et al., 1980; Murrin et al., 2007). This is confirmed by our studies that also found that the density of β-adrenergic receptors was lower in both the cortex and the prefrontal cortex on PND 13 than in adult rats, but similar to adult levels by PND 35.

It is interesting to note that DMI treatment increased α-1 receptor number when given to animals when those receptors were developmentally low (PND 9–13; Tables 3 and 6) and that it had the opposite effect when receptor number was then high (PND 21–35; Tables 5 and 6). Likewise, for α-2 receptors in the developmentally low density in the prefrontal cortex in PND 13 animals is up-regulated by DMI, whereas at PND 35 the lack of a DMI effect correlates with lack of a developmental difference. However, we feel that this is just coincidental, because it does not hold true for the α-2 receptors in the cortex at PND 13, nor for the β receptors under any of the conditions.

In conclusion, the results reported here clearly indicate that DMI affects cortical α-1- and α-2-adrenergic receptor regulation differently in juvenile compared with adult rats. This is likely to be due at least in part to the significant development changes in the noradrenergic nervous system in juvenile rats and to the immature mechanisms regulating receptor density. Because the adrenergic system also develops more slowly than the serotonergic system in humans, it is reasonable to surmise that alterations in α-adrenergic receptor regulation may be different in children compared with adults and that these differences contribute to the lack of efficacy of DMI as an antidepressant in children.
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References

Address correspondence to: Dr. David B. Bylund, Department of Pharmacology and Experimental Neuroscience, 985800 Nebraska Medical Center, Omaha, NE 68198-5800. E-mail: dbylund@umc.edu